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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,612	FARNEGARDH ET AL.	
	Examiner	Art Unit	
	Jae W. Lee, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *13-28,33,34 and 36-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,29-32 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 June 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *08/14/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

Claim(s) 1-39 are pending in this application.

Priority

A claim of priority to applications, PCT/IB03/06412, filed on 12/24/2003, and UNITED KINGDOM 0230177.8, filed on 12/24/2002, is acknowledged.

Election

Applicant's election without traverse of Group I, Claims 1-12, 29-32 and 35, and species election of SEQ ID NO: 1 in the response filed on 09/11/2007, is acknowledged.

Claim(s) 13-28, 33, 34 and 36-39, and SEQ ID NO: 2 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, Applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly pgs. 28-357 of the specification containing lists of atomic coordinates representing the disclosure of amino acid sequences, and therefore those lists should have a heading identifying the amino acid sequence with a proper sequence identifier number. Also, see Figure 5a and 5b which contain disclosure of amino acid sequences, and therefore those lists should be labeled with a proper sequence identifier number.

The specification is objected to because it has no mention of SEQ ID NOs when there are disclosures of polypeptide sequences SEQ ID NOs: 1 and 2 in the sequence listing filed on 06/23/2005. All SEQ ID NOs in the sequence listing must be properly described in the specification.

Appropriate correction is required.

Claim Objections

Claims 1-4, 6-10 and 29-31 are objected to because of the following informalities:

Claims 1-4, 6-10, 29 and 30 are objected to because the recitation of "LXRβ" can be improved with respect to form. The Examiner suggests the abbreviation "LXRβ" to be written out in full when used for the first time, i.e., "Liver X receptor beta."

Claim 7 are objected to because the recitations of "T0901317" and "GW3965" can be improved with respect to form. The Examiner suggests the abbreviations "T0901317" and "GW3965" to be written out in full when used for the first time, i.e., "N-(2,2,2-trifluoroethyl)-N-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-benzenesulfonamide," and "3-(3-(2-chloro-3-trifluoromethylbenzyl-2,2-diphenylethylamino)propoxy)phenylacetic acid," respectively.

Claims 9-10 are objected to because the phrase, "LBD," can be improved with respect to form. It is noted by the Examiner that this "LBD" will be interpreted as "ligand binding domain" in the interest of advancing prosecution.

Claim 9 is objected to because it can be improved with respect to form. The commas are missing after unit cell dimension a and b.

Claim 10 is objected to because it can be improved with respect to form. The symbol of "angstrom" is missing after each unit cell dimensions a, b, and c.

Claim 10 is objected to because it can be improved with respect to form. The space group "P21212" does not contain proper subscripts, i.e., "$P2_12_12$."

Claim 10 is objected to because the recitation of "LXRI3" contains a typographical error. It is noted by the Examiner that this "LXRI3" will be interpreted as "LXRβ" in the interest of advancing prosecution.

Claim 29 is objected to because the recitation of "Leu453, Trp457" can be improved with respect to form because said recitation is missing a conjunction between "Leu453," and "Trp457."

Claim 31 is objected to because it contains a non-elected invention, i.e., Figure 5b and SEQ ID NO: 2.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 29, 30 and 35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 8-10, 29 and 30 (4-7, 11, 12 and 35 dependent therefrom) recite the phrase, "LXRβ ligand binding domain" or "LBD," which are unclear and indefinite. It is unclear with respect to what is included and excluded from such a "ligand binding domain." It is noted by the Examiner that there is no clear definitions for these phrases in the specification. In the interest of advancing prosecution, said phrases are interpreted to encompass any amino acid residues of human LXRβ that are capable of binding any ligand.

Claim 7 recites the phrase, "the internal "LXRβ binding cavity," which is unclear and indefinite. It is unclear and confusing with respect to what is included and what is excluded from the scope of "the internal "LXRβ binding cavity." It is noted by the Examiner that there is no clear definition for this phrase in the specification.

Claim 2 recites the phrase, "an amino acid sequence having at least 95% identity with the sequence and which encodes for LXRβ ligand binding domain," which is unclear and indefinite. It is unclear with respect to how an amino acid sequence *encodes* for a protein, i.e., the LXRβ ligand binding domain.

Claim 29 recites the phrase, "the coordinate tables," which is unclear. It is unclear and confusing with respect to which coordinate tables Applicants are referring to, when the only "Table" disclosed in the specification is "Table 1" shown on pg. 24, which does not contain any coordinate.

It is suggested that Applicants clarify the meaning of noted phrases.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 29, 30, 32 and 35 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to (A) a genus of crystals comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) a genus of crystals of LXRβ LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°; (C) a genus of crystals of LXRβ LBD belonging to the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120°; (D) a genus of crystals of LXRβ LBD in complex with a coactivator peptide (TIF2 NR-box 1) belonging to the space group $P2_12_12$ and having the unit cell dimensions a = 89 +/- 3 Å, b = 91 +/- 3 Å, c = 131 +/- 3 Å, α=β=γ=90°; (E) a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435,

Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (F) a genus of crystallized compositions comprising at least 150 amino acid residues of the LXRβ ligand-binding domain.

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 further states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The specification discloses only two representative species of the genera of claimed crystals, comprising X-ray diffraction quality crystal of human liver X receptor beta consisting of the contiguous amino acid residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°, or alternatively has the space group P6122 and having the

unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120° that diffracts x-rays to a resolution of less than or equal to 3 angstroms. Other than these disclosed species, the specification fails to describe any additional representative species of the recited genera, which encompasses any crystals (including crystals that do not diffract X-rays at appreciable resolution for the structural characterization) comprising any 150 or more contiguous or non-contiguous amino acid residues of any LXRβ ligand binding domain, optionally complexed with any ligand, wherein said crystal can have widely variant space groups, unit cell dimensions and α, β, and γ angles, optionally wherein said crystal may produce any structural coordinates upon X-ray diffraction pattern analysis. Taken together, the genus of claimed crystals and isolated proteins encompasses widely variant species, having essentially any structure.

With regard to Claim 29, the genus of claimed crystallized molecules or molecular complexes is drawn to "any structure" because the structure of the crystallized molecules or molecular complexes are only limited by *two or more structure coordinates* from structure coordinates of any homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å (italicized for added emphasis). Therefore, the genus of claimed crystallized molecules or molecular complexes, in this case, encompasses widely variant crystallized molecules or molecular complexes comprising any two or more contiguous or non-contiguous amino acid residues from any homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more

than 1.5 Å when superimposed on the non-hydrogen atom positions of the corresponding atomic coordinates of human liver X receptor beta, optionally complexed with any ligand, wherein said crystalline form can have widely variant space groups, unit cell dimensions and α, β, and γ angles. Taken together, such broad genera of claimed crystals encompassing widely variant species, having essentially any structure, are not adequately supported by the disclosure of the instant application.

With regard to claim 6, it is noted by the Examiner that the above-mentioned genera of claimed crystals, further comprising "any ligand bound to any portion of LXRβ" encompass widely variant species, having essentially any structure, are not adequately supported by the disclosure of the instant application.

MPEP § 2163 states "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." As such, the single disclosed species of each genus as noted above fails to describe all members of each genus as encompassed by the claims.

Given the lack of description of a representative number of species, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

Claims 1-12, 29, 30, 32 and 35 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a crystal, comprising X-ray diffraction

quality crystal of human liver X receptor beta consisting of the contiguous amino acid residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°, or alternatively has the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120° that diffracts x-rays to a resolution of less than or equal to 3 angstroms, does not reasonably provide enablement for (A) any crystal comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) any crystal of LXRβ LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°; (C) any crystal of LXRβ LBD belonging to the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120°; (D) any crystal of LXRβ LBD in complex with a coactivator peptide (TIF2 NR-box 1) belonging to the space group $P2_12_12$ and having the unit cell dimensions a = 89 +/- 3 Å, b = 91 +/- 3 Å, c = 131 +/- 3 Å, α=β=γ=90°; (E) any crystallized molecule or molecular complex comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (F)

any crystallized composition comprising at least 150 amino acid residues of the LXRβ ligand-binding domain. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Undue experimentation would be required for a skilled artisan to practice the entire scope of the claimed invention. The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The breadth of the claims: Claims 1-18 are so broad as to encompass (A) any crystal comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) any crystal of LXRβ LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°; (C) any crystal of LXRβ LBD belonging to the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120°; (D) any crystal of LXRβ LBD in complex with a coactivator peptide (TIF2 NR-box 1) belonging to the space group $P2_12_12$ and having the unit cell dimensions a = 89 +/- 3 Å, b = 91 +/- 3 Å, c = 131 +/- 3 Å, α=β=γ=90°; (E) any crystallized molecule or molecular complex comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (F) any crystallized composition comprising at least 150 amino acid residues of the LXRβ ligand-binding domain with any number of additional amino acids at the N- and/or C-terminal end(s), optionally complexed with any ligand, and optionally having any space group/unit cell dimensions. The broad scope of the claims is not commensurate with the enablement provided by the disclosure. In this case the disclosure is limited to enabling a crystal, comprising X-ray diffraction quality crystal of

human liver X receptor beta consisting of the contiguous amino acid residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°, or alternatively has the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120° that diffracts x-rays to a resolution of less than or equal to 3 angstroms.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The state of the art at the time of the invention acknowledges a high level of unpredictability for making a protein crystal with an expectation that it is diffraction-quality. Branden et al. ("Introduction to Protein Structure Second Edition", Garland Publishing Inc., New York, 1999) teaches that "[c]rystallization is usually quite difficult to achieve" (p. 375) and that "[w]ell-ordered crystals...are difficult to grow because globular protein molecules are large, spherical, or ellipsoidal objects with irregular surfaces, and it is impossible to pack them into a crystal without forming large holes or channels between the individual molecules" (p. 374). Also, Drenth ("Principles of X-ray Crystallography," Springer, New York, 1995) teaches that "[t]he science of protein crystallization is an underdeveloped area" and "[p]rotein crystallization is mainly a trial-and-error procedure" (p. 1). One cannot predict *a priori* those conditions that will lead to the successful crystallization of a diffraction-quality crystal nor can one predict the space group symmetry or unit cell dimensions of the resulting crystal. See Kierzek et al. (*Biophys Chem* 91:1-20, 2001), which teaches that "each protein crystallizes

under a unique set of conditions that cannot be predicted from easily measurable physico-chemical properties" and that "crystallization conditions must be empirically established for each protein to be crystallized" (underline added for emphasis, p. 2, left column, top). See also McPherson et al. (*Eur. J. Biochem.* 189:1-23, 1990), which discloses (p. 13, column 2), "Table 2 lists physical, chemical and biological variables that may influence to a greater of less extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids" Table 2 of McPherson is a list of 25 different variables that can or do affect protein crystallization. As McPherson points out trying to identify those variables that are most important for each protein is extremely difficult and changing a protein by even a single amino acid can result is significant influences upon the change in which variables are important for successful crystallization. McPherson also goes on to teach, "[b]ecause each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual."

Thus, in view of these teachings, a skilled artisan would recognize that it is highly unpredictable as to whether or not one can achieve diffraction-quality crystals of other polypeptides comprising at least 150 amino acid residues of the LXRβ ligand binding domain or variants thereof, optionally having a desired space group and unit cell dimensions and α, β, and γ angles as broadly encompassed by the claims.

The amount of direction provided by the inventor; The existence of working examples: The specification discloses only a single working example of such a diffraction quality crystal, *i.e.,* a crystal, comprising X-ray diffraction quality crystal of human liver X receptor beta consisting of the contiguous amino acid residues 220 to 461 of SEQ ID NO: 1 complexed with GW3965, and T0901317, wherein said the crystal has the space group symmetry $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°, or alternatively has the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120° that diffracts x-rays to a resolution of less than or equal to 3 angstroms. Other than this working example, the specification fails to provide adequate guidance regarding (A) any crystal comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) any crystal of LXRβ LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°; (C) any crystal of LXRβ LBD belonging to the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120°; (D) any crystal of LXRβ LBD in complex with a coactivator peptide (TIF2 NR-box 1) belonging to the space group $P2_12_12$ and having the unit cell

dimensions a = 89 +/- 3 Å, b = 91 +/- 3 Å, c = 131 +/- 3 Å, α=β=γ=90°; (E) any crystallized molecule or molecular complex comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (F) any crystallized composition comprising at least 150 amino acid residues of the LXRβ ligand-binding domain with any number of additional amino acids at the N- and/or C-terminal end(s), optionally complexed with any ligand, and optionally having any space group/unit cell dimensions, which can be utilized for crystallization and structural studies in order to identify and synthesize new therapeutic compounds for treatment of atherosclerosis by inducing cholesterol efflux from macrophages/foam cells (see last paragraph of pg. 2 continued to pg. 3 of the specification).

The quantity of experimentation needed to make and use the invention based on the content of the disclosure: While methods of protein crystallography were known at the time of the invention, it was not routine in the art to screen all crystals (including those that do not diffract X-ray at appreciable resolution for the structural determination) comprising at least 150 amino acid residues of the LXRβ ligand binding domain, optionally having any space group and unit cell dimensions and α, β, and γ angles; of

any crystallized molecule or molecular complex comprising any binding pocket defined by any two or more contiguous or non-contiguous amino acid residues from any homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å when superimposed on the backbone atom positions of the corresponding atomic coordinates of the LXRβ ligand binding domain, as encompassed by the claims for those that will yield diffraction-quality crystals and to determine those crystals that represent biologically-relevant human liver X receptor structures.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make and use (A) any crystal comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) any crystal of LXRβ LBD belonging to the space group $P2_12_12_1$ and having the unit cell dimensions a = 59 +/- 3 Å, b = 100 +/- 5 Å, c = 176 +/- 3 Å, α=β=γ=90°; (C) any crystal of LXRβ LBD belonging to the space group P6122 and having the unit cell dimensions a = 59 +/- 3 Å, b = 59 +/- 3 Å, c = 294 +/- 3 Å, α=β=90°, γ=120°; (D) any crystal of LXRβ LBD in complex with a coactivator peptide (TIF2 NR-box 1) belonging to the space group $P2_12_12$ and having the unit cell dimensions a = 89 +/- 3 Å, b = 91 +/- 3 Å, c = 131 +/- 3 Å, α=β=γ=90°; (E) any crystallized molecule or molecular complex comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329,

Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350, Ile353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (F) any crystallized composition comprising at least 150 amino acid residues of the LXRβ ligand-binding domain with any number of additional amino acids at the N- and/or C-terminal end(s), optionally having any space group and unit cell dimensions and α, β, and γ angles as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of all crystals of (A)-(F) as mentioned above with any number of additional amino acids at the N- and/or C-terminal end(s), optionally having any space group and unit cell dimensions and α, β, and γ angles having the desired biological characteristics so that they can be utilized for crystallization and structural studies in order to identify and synthesize new therapeutic compounds for treatment of atherosclerosis by inducing cholesterol efflux from macrophages/foam cells, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-6, 11, 12, 29-32 and 35 are rejected under 35 U.S.C. § 102(e) as anticipated by Bledsoe et al. (US Patent Application No. 10/418,007, (effective filing date 04/26/2002))

The instant claim is drawn to (A) a genus of crystals comprising at least 150 amino acid residues of the LXRβ ligand binding domain; (B) a genus of crystallized molecules or molecular complexes comprising a binding pocket defined by the structure coordinates of human LXR/3 ligand binding domain amino acid residues Ser242, Phe268, Phe271, Thr272, Leu274, Ala275, Ser278, Ile309, Met312, Leu313, Glu315, Thr316, Arg319, Ile327, Phe329, Leu330, Tyr335, Phe340, Leu345, Phe349, Ile350,

Ile353, Phe354, His435, Gln438, Va1439, Leu442, Leu449, Leu453, Trp457, according to the coordinate tables or a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation form the backbone atoms of said amino acids of not more than 1.5 Å; and (C) a genus of crystallized compositions comprising at least 150 amino acid residues of the LXRβ ligand-binding domain; and (D) an isolated protein consisting essentially of the amino acid sequence shown from amino acid 220 to amino acid 461 in Figure 5a (SEQ ID NO: 1).

The reference of Bledsoe et al. teaches a crystallized ligand binding domain of human liver X receptor beta (LXRβ) consisting of contiguous amino acid residues 214-462 of SEQ ID NO: 4, which includes helix 12 (Pro450 to Ile-456) bound to ligands, i.e., T317, SRC1 and EPC, which is capable of diffracting X-ray at the resolution of 2.3 angstrom (see pg. 5, paragraph [0027], and Tables 1 and 2 on pg. 27). Therefore, the above-mentioned teachings anticipate claims 1, 2 (in the recitation of "an amino acid sequence having at least 95% identity with the sequence and which encodes for a LXRβ ligand binding domain"), 3-6, 11, 12, and 29-31. Claim 29 is included in this rejection because the crystallized LXRβ defined by the structural coordinates is not limited to a specific set of coordinates, i.e., "according to the coordinate tables," in addition to the broad scope of the recitation, "a homologue of said molecule or molecular complex wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å," which can be any two or more amino acid residues recited in claim 29. The reference further teaches that said receptor fragment was attached to "a thrombin cleavable his-tag" (see pg. 24,

paragraph [0289]), thereby anticipating claim 32. The reference also discloses the three-dimensional model of the ligand binding domain (LBD) or ligand binding pocket binding a ligand in Figures 2, 3, 6A and 6B (see also the Figure legends).

It is noted by the Examiner that the SEQ ID NO: 4 of Bledsoe et al. and Applicant's SEQ ID NO: 1 is identical (see below and also SCORE result 5 under 20071016_153205_us-10-540-612-1.rag). Therefore, Applicants' claimed is anticipated by the teachings of Bledsoe et al.

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XX
PS   Claim 44; SEQ ID NO 4; 198pp; English.
XX
CC   The invention relates to a crystalline form comprising substantially pure
CC   liver X receptor (LXR) ligand binding domain polypeptide, ligand, and/or
CC   coactivator polypeptide. The crystalline LXR is useful for designing
CC   modulator that selectively modulates the activity of a NR polypeptide
CC   compared to other polypeptides. Crystalline LXR is useful for screening
CC   several compounds for a modulator of a NR ligand binding domain
CC   polypeptide. The test sample is bound substrate. The test sample is
CC   synthesised directly on substrate. The coregulator comprises SRC1
CC   polypeptide. The present sequence represents the amino acid sequence of
CC   human liver X receptor LXR beta.
XX
SQ   Sequence 461 AA;

  Query Match             100.0%;  Score 2418;  DB 5;  Length 461;
  Best Local Similarity   100.0%;  Pred. No. 6.2e-159;
  Matches  461;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MSSPTTSSLDTPLPGNGPPQPGAPSSSPTVKEEGPEPWPGGPDPDVPGTDEASSACSTDW 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSSPTTSSLDTPLPGNGPPQPGAPSSSPTVKEEGPEPWPGGPDPDVPGTDEASSACSTDW 60

Qy         61 VIPDPEEEPERKRKKGPAPKMLGHELCRVCGDKASGFHYNVLSCEGCKGFFRRSVVRGGA 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 VIPDPEEEPERKRKKGPAPKMLGHELCRVCGDKASGFHYNVLSCEGCKGFFRRSVVRGGA 120

Qy        121 RRYACRGGGTCQMDAFMRRKCQQCRLRKCKEAGMREQCVLSEEQIRKKKIRKQQQQESQS 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 RRYACRGGGTCQMDAFMRRKCQQCRLRKCKEAGMREQCVLSEEQIRKKKIRKQQQQESQS 180

Qy        181 QSQSPVGPQGSSSSASGPGASPGGSEAGSQGSGEGEGVQLTAAQELMIQQLVAAQLQCNK 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 QSQSPVGPQGSSSSASGPGASPGGSEAGSQGSGEGEGVQLTAAQELMIQQLVAAQLQCNK 240

Qy        241 RSFSDQPKVTPWPLGADPQSRDARQQRFAHFTELAIISVQEIVDFAKQVPGFLQLGREDQ 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 RSFSDQPKVTPWPLGADPQSRDARQQRFAHFTELAIISVQEIVDFAKQVPGFLQLGREDQ 300

Qy        301 IALLKASTIEIMLLETARRYNHETECITFLKDFTYSKDDFHRAGLQVEFINPIFEFSRAM 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 IALLKASTIEIMLLETARRYNHETECITFLKDFTYSKDDFHRAGLQVEFINPIFEFSRAM 360

Qy        361 RRLGLDDAEYALLIAINIFSADRPNVQEPGRVEALQQPYVEALLSYTRIKRPQDQLRFPR 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 RRLGLDDAEYALLIAINIFSADRPNVQEPGRVEALQQPYVEALLSYTRIKRPQDQLRFPR 420

Qy        421 MLMKLVSLRTLSSVHSEQVFALRLQDKKLPPLLSEIWDVHE 461
              |||||||||||||||||||||||||||||||||||||||||
Db        421 MLMKLVSLRTLSSVHSEQVFALRLQDKKLPPLLSEIWDVHE 461
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Conclusion

Claims 1-12, 29-32 and 35 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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PRIMARY EXAMINER